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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/869,060	FRANTZEN, FRANK	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-91* is/are rejected.

7)☒ Claim(s) *71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 10/3/07, is acknowledged and has been entered. Claims 24-57 were canceled. New claims 58-91 were added. Accordingly, claims 58-91 are currently pending and subject to examination below.

Objections/Rejections Withdrawn

2. The objection to the specification has been obviated by the amendments thereto.

3. The objections to claims 24, 26, 35-36, 38, 44-45, 52-53, and 57 have been mooted by Applicant's cancellation thereof.

4. Similarly, the rejections of claims 24-57 are moot in light of the claims' cancellation.

Claim Objections

5. Claim 71 is objected to because of the following informalities:

6. There is a typographical error in the preamble of claim 71 in that the phrase "A homocysteine assay reagent kit" is apparently duplicated.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 58-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Written Description

9. New claims 58-59 and 70-71 recite "a polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MD".

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

In the instant case, the genus of polyhaptens is identified only by reference to molecular weight. Although the polyhaptens all share the common feature of having hapten moieties, the haptens may be of any structure or molecular composition. As such, the genus of polyhaptens is not described in terms of any common partial structure. Without such identifying characteristics, such a large genus cannot be readily envisaged because the characteristics of the genus are not known.

The specification discloses that the hapten moieties should be "the same as or similar to at least part of the analyte" (page 8, first paragraph). However, the claims do not currently require any structural relationship at all between the haptens and the analyte (in this case, the homocysteine conversion product SAH). Since the assay method involves competition between SAH (formed from homocysteine in the sample) and the polyhapten for binding to the primary antibody, it is clear that the hapten must be SAH (or a structural analog thereof that also cross-reacts with an anti-SAH antibody) in order to possess this function.

Therefore, one skilled in the art would not envisage possession of methods of using polyhaptens having *any* type of hapten moiety, since the specification discloses that the assay method involves competition between hapten and SAH, therefore requiring the hapten to be one that would also cross-react with an anti-SAH antibody.

Moreover, with the exception of SAH, Applicant has not described what other hapten moieties would possess the necessary functional characteristics. Applicant has not described what parts of SAH would be responsible for antibody binding (i.e., what portions of this molecule are antigenic), and therefore has not described what variants or fragments of SAH could serve as hapten moieties. As such, there is no disclosed correlation between function (ability to compete with an antibody that also binds SAH) and structure that is shared by the members of the genus of polyhaptens. In particular, Applicant has not adequately described what haptens other than SAH would cross-react with an anti-SAH antibody.

It is known that even small changes in the antigen structure can profoundly affect antibody-antigen interaction (see Harlow & Lane, "Antibodies: A Laboratory Manual" (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pages 23-26; especially at

page 26). In light of this recognized unpredictability in changing antigen structure while retaining antibody binding, it is evident that the disclosure of a single species (polyhaptens having SAH as the hapten moiety) fails to adequately describe the claimed genus of polyhaptens, particularly given the substantial variability in structure among the polyhaptens encompassed by the claims. The claimed genus of polyhaptens cannot be readily envisaged because it is not known what hapten moieties other than SAH would possess the necessary functional characteristics. For all of these reasons, the specification fails to convey evidence of the currently claimed genus of polyhaptens, and therefore fails to adequately describe the claimed assay method.

4. Claims 58-59 and 70-71 recite a "primary antibody capable of binding to said polyhapten" and a "secondary antibody capable of binding to said complex". Claims 60, 69, 72, 78-79, 86-87 and 91 also refer to primary and/or secondary antibodies.

It is noted that the specification defines the term "**antibody**" in such a way so as to encompass "single chain antibodies, antibody fragments (e.g. Fab fragments), and oligopeptides and oligonucleotides" (page 5, the first full paragraph; see also page 10, the first full paragraph).

Thus, the claims are not limited to antibodies *per se* since the term "antibody" as it is employed in the claims would include not only antibodies *per se*, but also non-antibody oligopeptides and oligonucleotides.

The specification provides a description of primary antibodies that are specific for SAH and of secondary anti-mouse IgG antibodies, and outlines art-recognized techniques for producing such antibodies (see page 5). However, the specification does not provide a written

description to support evidence of possession of the claimed genus of "primary antibodies" that are capable of binding to a polyhapten in light of Applicant's definition of "antibody". Likewise, the specification does not provide an adequate written description of "second antibodies" that are capable of binding to the polyhapten-primary antibody complex that is commensurate with the scope of the claims.

The specification fails to describe any non-antibody oligopeptides or oligonucleotides with any particularity. The specification does not disclose any partial structure or relevant identifying characteristics that would be shared by the members of the genus of "antibodies" that bind to polyhapten and/or polyhapten-antibody complex. There is no disclosed correlation between any partial structure (for example, a polynucleotide binding motif) and function (ability to bind to polyhapten and/or polyhapten-antibody complex). The specification does not describe any methods of making any non-antibody oligopeptide or oligonucleotide "antibodies" against a polyhapten or polyhapten complex. The specification fails to disclose any partial structure, relevant identifying characteristics, or method of making "antibodies" that are RNA, DNA or proteins other than antibodies *per se*.

The courts have stated that "as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." *Noelle v. Lederman*, 355 F.3d at 1349 (Fed. Cir. 2004, emphasis in the original). Although *Noelle* relates to antibodies *per se* and not to detecting methods using such antibodies, the holdings of those cases are also applicable to claims such as those at issue here. A

disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In the instant case, Applicant has also failed to describe the claimed antibodies in terms of any fully characterized antigen, since while antibodies *per se* that are specific for SAH as the hapten moiety are adequately described, the instant claims are not limited to polyhaptens that possess any particular common structure (such as SAH). Although the members of the genus of polyhaptens all contain at least one hapten moiety, this does not correspond to any common structure linking the members of the genus, since the hapten itself may be of any disclosed or undisclosed structure. The polyhapten therefore does not constitute a "fully characterized antigen" because as currently recited, it may be of any structure so long as it falls within the recited molecular weight. Therefore, the recitation that the primary antibody binds to polyhapten fails to constitute adequate written description because the polyhapten antigens are also not adequately described. An unknown cannot be adequately described by reference to another unknown.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of "antibodies".

Scope of Enablement

10. Claims 58-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assay methods using polyhaptens comprising S-adenosine homocysteine (SAH) as the hapten moieties, does not reasonably provide enablement for assay

methods that use any polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MD. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to a competition immunoassay method for measuring homocysteine, in which homocysteine in the sample is detected indirectly by detecting the amount of a complex formed between a primary antibody and a polyhapten. Homocysteine in the sample is converted to SAH, which then competes with the polyhapten for binding to the primary antibody. Thus, the amount of primary antibody-polyhapten complex detected would be inversely related to the amount of homocysteine in the sample.

The specification discloses that the polyhapten bears hapten moieties that are the same as or similar to at least part of the analyte (in this case, the homocysteine conversion product SAH). See page 8, the first paragraph.

However, the claims broadly recite "a polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MDa". Thus, there is no requirement that the polyhapten be of any particular structure, so long as it falls within the indicated size range. Notably, the claims do not require that the hapten moieties on the polyhapten bear any structural relationship to the analyte being detected (SAH).

The specification fails to provide sufficient guidance with regard to how to use polyhaptens that have no structural relationship to SAH in the claimed method of measuring homocysteine. It is unclear how a polyhapten having no structures or epitopes in common with SAH (as would be encompassed by the claims) could be successfully used in a competition

immunoassay to detect homocysteine, since an antibody that recognized SAH would not be expected to also recognize a polyhapten of entirely different structure.

Furthermore, although the specification discloses working examples in which polyhaptens having SAH as the hapten moiety were used, there are no working examples in which any other type of hapten moiety was used. The disclosed assay method requires that the polyhapten compete with SAH (produced from homocysteine in the sample) for binding to the same primary antibody. The specification fails to provide guidance with respect to what hapten moieties other than SAH would cross-react with an anti-SAH primary antibody.

The prior art teaches that even small changes in the antigen structure can profoundly affect antibody-antigen interaction (see Harlow & Lane, pages 23-26; especially at page 26, the first full paragraph). Therefore, the prior art recognized unpredictability associated with changing antigen structure while successfully retaining antibody binding.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id.

In the instant case, such reasonable detail is lacking. Although it is suggested in the instant specification to use other hapten moieties that are "similar to at least part of the analyte" (page 8), the specification fails to provide guidance with regard to what parts of the analyte (SAH) would be critical for antibody binding, and what other parts might be successfully varied,

modified or removed in order to create such other hapten moieties that are "similar to at least part of" SAH. Applicant has not described what variants, analogs, or fragments of SAH would still retain the necessary function of competing with SAH for binding to the same antibody.

Given the breadth of the polyhaptens that would be encompassed by the claims, as well as the recognized unpredictability in the field, the disclosure of polyhaptens that comprise SAH as hapten moieties and the general invitation to employ other hapten moieties fails to enable the skilled artisan to use any type polyhapten to detect homocysteine. See *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...".

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 58-91 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: that the hapten moieties of the polyhapten are the same as or similar to at least part of the analyte (the homocysteine conversion product SAH).

The specification discloses that the assay method involves competition between the analyte (SAH converted from homocysteine in the sample) and the polyhapten for binding to the primary antibody (see the paragraph bridging pages 7-8). In order for the polyhapten to compete

for binding with the analyte, it would have to bear hapten moieties that are "the same as or similar to" SAH.

However, the claims as instantly amended recite only "a polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MD". There is no reflection in the claims that the polyhapten bears any structural similarity to SAH, which is essential to the performance of the claimed competition assay.

Applicant is reminded that claim terminology introduced should comply with the requirements of 35 U.S.C. 112, first and second paragraph; terminology used by the Examiner in the above explanation should not be taken as an indication that such terminology is necessarily in compliance with these requirements.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 58-60, 63-64, 66-67, 70-73, 75-76, 79, 82-85, and 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantzen et al. ("Enzyme conversion immunoassay for determining total homocysteine in plasma or serum" *Clinical Chemistry* 44:2 (1998), 311-316) in view of Zuk et al. (4,208,479).

Frantzen et al. teach a competitive immunoassay method for determining homocysteine (Hcy) in plasma or serum substantially as claimed, in which a sample is contacted with the

following reagents: adenosine, reducing agent (DTT), a "first enzyme" (SAH hydrolase or SAHase), a "second enzyme" (adenosine deaminase or Adoase) capable of converting adenosine to inosine, polyhapten (BSA-S-adenosyl-L-homocysteine (SAH) conjugate), primary antibody capable of binding to polyhapten (mouse anti-SAH antibody), second antibody capable of binding to polyhapten-first antibody complex (anti-mouse antibody). See the entire document, in particular the abstract; p. 311-312, the sections "Materials and Methods" and "Assay Method"; and Figure 2. The reference further teaches photometrically detecting the complex by spectrophotometric reading (Figure 2).

Although Frantzen et al. is silent as to whether the BSA-SAH polyhapten is "a polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MDa", this same polyhapten is also disclosed in the instant specification (see page 13). It is therefore presumed that the BSA-SAH polyhapten necessarily possess the recited molecular weight characteristics. See MPEP 2112.01.

Frantzen et al. further teach a blocking solution (see p. 312, "Coating of microtiter plates"), which would be considered to be an "agent which promotes precipitation" of the polyhapten-antibody complex in that the blocking agent would reduce nonspecific binding to the microtiter plates, and thus promote formation and precipitation of the specific complex. The reference also teaches heparin (see p. 313, left column, "Blood samples"), which is disclosed an example of an agent promoting precipitation (see the instant specification at page 6). The reference also teaches thimerosal, which is used as an inhibitor of SAHase in order to remove excess adenosine (p. 316, left column). This would also be considered to be an agent that promotes precipitation of the polyhapten-antibody complex since the reference discloses that the

anti-SAH antibody can cross-react somewhat with adenosine (ibid), such that by removing excess adenosine the thimerosal would promote formation and precipitation of the antibody-polyhapten complex. Thus, given the broadest reasonable interpretation of an "agent which promotes precipitation", any of the above reagents would read on the claim limitation.

Frantzen et al. differs from the claimed invention in that although it teaches the same reagents claimed, it fails to specifically teach mixing the reagents together into two or three different reagent mixtures in the specific manner claimed.

Rather, the Frantzen et al. reference teaches mixing the sample with a reagent mixture of adenosine, reducing agent, and first enzyme, followed by addition of second enzyme (see Figure 2). This sample is then contacted with polyhapten (coated on a microtiter plate), followed by sequential addition of primary and second antibody (ibid and p. 312, "The enzyme assay" and "The immunoassay").

However, the prior art recognized the value of combining together multiple reagents needed for performing an assay into reagent mixtures. For example, Zuk et al. teach that reagents for performing an assay can be combined together in a kit for substantial convenience as well as enhancement in accuracy (column 22, lines 20-68). In particular, the reference teaches that *it is desirable to combine as many reagents as possible in a single vessel*, with certain provisos, for example that the reagents mixed must not adversely interact with each other, as would occur if enzymes and their substrates were mixed. The reagents can be provided in aqueous form as concentrated solutions or as dilute ready to use solutions. This allows for accurate transfer and a predetermined final concentration and ratio of reagents. Besides the reagents necessary for the assay, there will normally be other additives, e.g. various stabilizers and preservatives.

Therefore, in light of the prior art teachings of Zuk et al. (for example), it would have been obvious to one of ordinary skill in the art at the time of the invention to combine together the necessary reagents for performing the homocysteine assay of Frantzen et al. for the art-recognized benefits of convenience and improvement in assay accuracy. Keeping in mind the art-recognized importance of ensuring that the reagents mixed together are stable and do not adversely interact with each other (i.e., enzymes and their substrates should not be provided together), as taught for example by Zuk et al., it would have been a matter of routine skill in the art to combine the reagents together in the particular manner(s) claimed, given the limited number of reagents and thus the limited number of possible ways in which the reagents may be combined together while providing SAHase separately from its substrate adenosine. The selection of any order of mixing ingredients is prima facie obvious (MPEP 2144.04).

With respect to claims 66, 75, and 89, Zuk et al. teach that besides reagents necessary for the assay, other additives are normally included, such as serum albumin, which acts as a stabilizer (column 22, lines 53-62). Therefore, it would have been obvious to include serum albumin as taught by Zuk et al. in the reagent mixture(s) of Frantzen et al. and Zuk et al. in order to stabilize the reagents. It is noted that albumin is disclosed in the specification as an example of a carrier protein according to the instant invention at page 7.

With respect to claims 67, 76, and 90, Frantzen et al. teach a backbone structure (BSA) onto which the SAH moieties are conjugated (p. 311, right column, the last paragraph).

15. Claims 58-64, 66-67, 70-73, 75-76, 79-85, and 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sundrehagen et al. (WO 93/15220) in view of Zuk.

Sundrehagen et al. teach methods and kits for assaying homocysteine in a sample (e.g. blood, plasma or urine), for example by competitive immunoassay, in which the test sample is contacted with adenosine and SAH hydrolase (see in particular the abstract; page 3, the last paragraph to page 9; and pages 23-25). As one example, a polyhapten can be provided that competes with the analyte (homocysteine) for binding to a particle-bound antibody, which is then detected by turbidimetric or nephelometric measurement (page 14). The method employs the following reagents: a polyhapten, which can be SAH itself (p. 16-17), a "first enzyme" that is SAH hydrolase, a second enzyme capable of converting adenosine (adenosine deaminase or adenosine kinase), adenosine or an adenosine analog, a primary antibody capable of binding to the polyhapten (anti-SAH antibodies; see Example 7 and pages 16 and 34 in particular), and a reducing agent (p. 7-8 and 15). Although Sundrehagen et al. do not specifically mention that the polyhapten is "a polyhapten having at least one hapten moiety per 100kD of its molecular weight and having a molecular weight in the range 500 kD to 3 MDa", the reference teaches SAH conjugated to BSA, which is also disclosed in the instant specification (see page 13). It is therefore presumed that the BSA-SAH polyhapten of Sundrehagen et al. necessarily possess the recited molecular weight characteristics. See MPEP 2112.01.

The reference further teaches photometric detection of antibody:polyhapten complexes, for example by turbidimetric or nephelometric measurement as noted above (see for example the paragraph bridging p. 3-4 and pages 14 and 24-25).

Sundrehagen et al. differs from the claimed invention in that although it teaches the same reagents claimed, it fails to specifically teach mixing the reagents together into two or three

different reagent mixtures in the specific manner claimed. The reference also fails to specifically teach kits comprising stable *aqueous* mixtures of the reagents.

However, the prior art recognized the value of combining together multiple reagents needed for performing an assay into reagent mixtures. For example, Zuk et al. (discussed above) teach that reagents for performing an assay can be combined together in a kit for substantial convenience as well as enhancement in accuracy (column 22, lines 20-68). In particular, the reference teaches that *it is desirable to combine as many reagents as possible in a single vessel*, with certain provisos, for example that the reagents mixed must not adversely interact with each other, as would occur if enzymes and their substrates were mixed. The reagents can be provided in aqueous form as concentrated solutions or as dilute ready to use solutions. This allows for accurate transfer and a predetermined final concentration and ratio of reagents. Besides the reagents necessary for the assay, there will normally be other additives, e.g. various stabilizers and preservatives.

Therefore, in light of the prior art teachings of Zuk et al. (for example), it would have been obvious to one of ordinary skill in the art at the time of the invention to combine together the necessary reagents for performing the homocysteine assay of Sundrehagen et al. for the art-recognized benefits of convenience and improvement in assay accuracy. Keeping in mind the art-recognized importance of ensuring that the reagents mixed together are stable and do not adversely interact with each other (i.e., enzymes and their substrates should not be provided together), as taught for example by Zuk et al., it would have been a matter of routine skill in the art to combine the reagents together in the particular manner(s) claimed, given the limited number of reagents and thus the limited number of possible ways in which the reagents may be

combined together while providing SAHase separately from its substrate adenosine. It would have been further obvious to provide the reagent mixtures in aqueous form for the convenience of a ready-to-use format, as taught by Zuk et al. The selection of any order of mixing ingredients is prima facie obvious (MPEP 2144.04).

One would have a reasonable expectation of success because Sundrehagen et al. teach that the necessary reagents may be added to the reaction mixture either in a sequential manner or simultaneously (see page 23).

With respect to claims 60, 72, 75, and 87, Sundrehagen et al. also teach a secondary antibody (sheep anti-mouse IgG) that specifically binds to the primary antibody (which is a mouse IgG anti-SAH antibody) (see page 34).

With respect to claims 62 and 81, Sundrehagen et al. teach that detection may be performed either at the reaction end point or alternatively, either at one or more fixed time points or via kinetic measurement (page 22).

With respect to claims 66, 75, 84, and 89, Sundrehagen et al. teach that carrier proteins can be added as additives to enhance SAH hydrolase stability during storage or during the assay itself (see the paragraph bridging p. 15-16). Zuk et al. also teach that besides reagents necessary for the assay, other additives are normally included, such as serum albumin, which acts as a stabilizer (column 22, lines 53-62). Therefore, it would have been further obvious to include serum albumin as taught by Zuk et al. in the reagent mixture(s) of Frantzen et al. and Zuk et al. in order to stabilize the reagents. It is noted that albumin is disclosed in the specification as an example of a carrier protein according to the instant invention at page 7.

With respect to claims 64, 73, 83, and 88, Sundrehagen et al. teach sucrose (see the paragraph bridging pages 15-16), which is a polysaccharide; polysaccharides are disclosed as examples of suitable agents according to the instant specification at page 6.

With respect to claims 67, 76, 85, and 90, Sundrehagen et al. teach conjugating the hapten to BSA or hemocyanin (page 16).

16. Claims 64-65 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantzen et al. in view of Zuk et al., or alternatively over Sundrehagen et al. in view of Zuk et al. as applied to claims 24 and 36 above, and further in view of either Karl et al. (US 6,210,975) or Lin et al. (US 4,298,592, Applicant's IDS of 6/25/01).

Frantzen et al., Zuk et al., and Sundrehagen et al. are as discussed above, which fail to specifically teach polyethylene glycol as a component of one of the reagent mixtures.

Karl et al. teach immunoassay methods for the detection of analytes, in which polyethylene glycol is added to the reaction mixture in order to reduce error due to the hook effect (see especially the abstract and columns 1-2). Nephelometric and turbidimetric detection is also specifically taught (the abstract).

Lin et al. also teach providing polyethylene glycol having a molecular weight of from about 2,000 to about 10,000 in order to accelerate immunoprecipitation reactions (column 2, lines 36-68).

Therefore, it would have been obvious to include polyethylene glycol in the reagent mixtures of Frantzen et al. and Zuk et al. and/or Sundrehagen et al. and Zuk et al. in order to

reduce sources of error due to the hook effect in an immunoassay as taught by Karl et al. and/or in order to accelerate the reaction as taught by Lin et al.

17. Claims 68 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantzen et al. in view of Zuk et al., or alternatively over Sundrehagen et al. in view of Zuk et al. as applied to claims 67 and 76 above, and further in view of Yanaihara et al. (US 4,855,406).

The references are as discussed above. Sundrehagen et al. teach polyhaptens having a hapten such as SAH conjugated to BSA or hemocyanin (page 16). Frantzen et al. also teach the backbone structure BSA onto which the SAH moieties are conjugated (p. 311, right column, the last paragraph).

However, the references fail to specifically teach that the backbone structure is porcine thyroglobulin.

Yanaihara et al. teach carrier molecules to which haptens may be bound (column 7, lines 24-50). In particular, the reference teaches that both bovine serum albumin (as taught by Sundrehagen et al. and Frantzen et al.) as well as porcine thyroglobulin are known carriers to which haptens may be bound. The Courts have ruled that art-recognized equivalence between embodiments provides a strong case of obviousness in substituting one material for another. See MPEP 2144.06.

Because Yanaihara et al. teach that bovine serum albumin and porcine thyroglobulin are recognized as equivalents applied for the same purpose (binding to haptens), it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute porcine thryoglobulin, as taught by Yanaihara et al., for bovine serum albumin of Frantzen et al. or

Sundrehagen et al. in the method and kit of Frantzen et al. and Zuk et al. or of Sundrehagen et al. and Zuk et al.

18. Claims 69, 78, 86, and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantzen et al. in view of Zuk et al., or alternatively over Sundrehagen et al. in view of Zuk et al. as applied to claims 24-25 and 36-37 above, and further in view of either Hideo et al. (JP 04329357, Applicant's IDS of 6/25/01) or de Steenwinkel et al. (US 4,362,531).

The references are as discussed above, which fail to specifically teach a chaotropic salt.

However, Hideo et al. teach adding a chaotropic salt (urea, thiocyanate, or guanidine HCl) to a reaction mixture in order to reduce nonspecific binding in an immune nephelometric reaction (see the English abstract provided).

de Steenwinkel et al. also teach adding one or more chaotropic or chaotropic-like agents to a reaction mixture in order to reduce non-specific protein interaction interferences in particle agglutination immunoassays (see especially the abstract and columns 2-4 in particular). The chaotropic agents include chaotropic salts (column 3, lines 45-65).

Therefore, it would have been obvious to one of ordinary skill in the art to include chaotropic salts as taught by either Hideo et al. or de Steenwinkel et al. in the reaction mixtures of Frantzen et al. and Zuk et al., or alternatively of Sundrehagen et al. and Zuk et al. One would be motivated to do this in order to reduce nonspecific binding.

Response to Arguments

5. Applicant's arguments, filed 10/3/07, have been fully considered. Although the arguments are technically moot in light of the cancellation of all previously pending claims, certain of the arguments will be addressed below as they appear to have relevance to the newly presented claims.

6. With respect to the rejections under § 112, 1st paragraph as failing to comply with the written description requirement in relation to Applicant's definition of the term "antibody" (see above and the previous Office action at pages 5-7, item 13), Applicant argues that the enclosed description amendment deletes the terms "oligopeptides" and "oligonucleotides" (Reply, page 13). However, no corresponding amendment to the specification was found as part of Applicant's Reply. Therefore, the rejection is maintained for reasons of record as set forth above.

Regarding the "antibody fragments" encompassed in Applicant's definition of the term "antibody", Applicant's arguments that it was well known in the art at the time of the invention what portions of antibodies bind antigen are persuasive (see Reply, page 13, last two paragraphs to page 14, the first full paragraph) and accordingly, this aspect of the rejection has been withdrawn.

19. With respect to the rejections under § 103(a) as being unpatentable over Frantzen et al. in view of Zuk et al., Applicant's arguments (see pages 15-19) have been fully considered but are not persuasive of error. Applicant argues that in Frantzen, the polyhapten is not in soluble form but is attached to the surface of a microtiter plate. This is not found persuasive because the claims fail to exclude that the polyhapten is immobilized. In fact, the instant specification states that the polyhapten may be immobilized to a solid carrier (page 9, the first full paragraph).

Although the claims recite that the polyhapten is part of an "aqueous" reagent mixture, given the broadest reasonable of this terminology, this could convey simply that the mixture includes a liquid rather than being provided in dried form. It does not necessarily rule out reagent components that are immobilized. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the polyhapten must be soluble and not immobilized to a solid phase) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant further argues that the method of Frantzen requires further binding and enzymatic reactions to generate a signal (Reply, paragraph bridging pages 16-17). However, because the instant claims employ open transitional language ("comprising"), such additional elements are not excluded.

Applicant further argues that Frantzen discloses a homocysteine assay that has been optimized, but nonetheless requires multiple aqueous reagents, therefore teaching away from the present method involving a reduced number of reagents (Reply, page 17). This is not found persuasive because although Frantzen et al. happen to employ a larger number of reagents, this does not rise to the level of a teaching away, as the reference does not disparage or discourage the skilled artisan from using a fewer number of reagents.

Applicant further argues that Zuk relates to a specific type of immunoassay, apparently arguing that one of ordinary skill in the art would not understand the teachings to be applicable to any type of assay. This is not found persuasive because such statements by Zuk as "[i]n

performing assays it is a matter of substantial convenience, as well as providing significant enhancement in accuracy to provide the reagents combined in a kit" (column 22) do reasonably convey that the advantages of kits for assays in general was known in the art at the time the invention is made. In addition, the test for obviousness involves consideration of what the combined teachings, as opposed to the individual teachings, of the references would have suggested to those of ordinary skill in the art. In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991); In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981).

Applicant apparently acknowledges that Zuk provides a desire to reduce the number of separate reagents in a known assay method (Reply, page 18, last paragraph) but argues that there are many possible assay formats that could be used, such that the currently claimed combination is non-obvious (Reply, pages 18-19). This is not found persuasive for reasons of record. In particular, given the known desire to reduce the number of reagents in an assay, as well as the knowledge in the art about what types of reagents can be successfully mixed together and what types can not (as taught for example by Zuk et al.), it is maintained that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention given the finite number of ways in which the reagents of Frantzen et al. may be combined.

20. With respect to the rejections under § 103(a) as being unpatentable over Sundrehagen et al. in view of Zuk et al., Applicant further argues that Zuk does not address homocysteine (Reply, page 20). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In*

re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Sundrehagen et al. reference has been relied upon for this teaching.

Applicant also argues for the large number of possible formats, method and reagents that the skilled worker must investigate in order to reduce the number of stable reagents required to the claimed number, and further argues that Zuk provides no specific teaching as to how to combine the reagents into single mixtures without violating the order in which they must be applied (Reply, especially at page 20). This is not found persuasive because the "[A]nalysis [of whether the subject matter of a claim is obvious] need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR Int'l Co. Teleflex, Inc., 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007) quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); see also DyStar Textilfarben GmBH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1361, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006)("The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.").

In the instant case, as discussed above with respect to Frantzen et al., Zuk et al. does provide guidance with respect to what reagents may be successfully mixed together. When taken together with Sundrehagen et al., which teaches a finite number of reagents and methods for homocysteine assay, it is maintained for reasons of record that it would have been obvious to arrive at the claimed invention given the limited number of possible ways in which such known reagents may be combined together.

Finally, in regards to the patentability of the product claims, Applicant is reminded that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, for example, arguments as to the order in which the reagents must be applied (see, e.g., the Reply at page 20) are therefore not applicable to the product claims since they are directed to the intended use of the claimed reagent mixtures and would not convey a structural difference therein.

Applicant does not separately argue the limitation of the dependent claims (see Reply, pages 20-21).

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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